

5 We Claim:

1. A method for inferring a gene network, comprising
  - (a) providing an inferential model of possible gene networks of an organism including defining a search space;
  - (b) selecting a biologically relevant subspace of said search space; and
  - (c) calculating an optimal solution in said selected subspace by repeatedly applying an algorithm that computes small gene networks optimally.
  
2. The method of claim 1, wherein said inferential model is a Bayesian network estimation model.
  
3. The method of claim 1, wherein said biologically relevant subspace includes genes relating to a metabolic pathway of said organism.
  
- 20 4. The method of claim 1, wherein said algorithm comprises the steps:
  - (a) compute  $F(g, \phi) = s(g, \phi)$  for all  $g \in G$ ;
  - (b) for all  $A \subseteq G$ ,  $A \neq \phi$  and all  $g \in G$  compute  $F(g, A)$  as  $\min\{s(g, A), \min_{a \in A} F(g, A - \{a\})\}$ ;
  - (c) set  $M(\phi) = \phi$ ;
  - 25 (d) for all  $A \subseteq G$ ,  $A \neq \phi$ , do the following steps:
    - (i) compute  $g^* = \arg \min_{g \in A} (F(g, A - \{g\}) + Q^{A - \{g\}}(M(A - \{g\})))$ ; and
    - (ii) for all  $1 \leq i < |A|$ , set  $M(A)(i) = M(A - \{g^*\})(i)$ , and  $M(A)(|A|) = g^*$ ;
  - (e) return  $Q^G(M(G))$ .
  
- 30 5. The method of claim 4, wherein said algorithm is modified according to the steps of:
  - (a) in the computation of F in Step 1 and Step 2, compute only  $F(g, A)$  for all  $g \in S_i$  and all  $A \subseteq C_g$ ; and

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5 (b). replace the term  $F(g, A - \{g\})$  in Step 4a by  $F(g, (C_g = S_i) \cup (C_g \cap A))$ .

6. The method of claim 1, wherein an optimal network  $N$  has a definition:  $score(N) = \sum_{g \in G} s(g, P^N(g))$ .

10 7. The method of claim 1, wherein said algorithm comprises the steps:

- (a) cluster genes in  $G$  such that no cluster is larger than  $c$  genes;
- (b) sort the clusters by decreasing size:  $C_1, \dots, C_n$ ;
- (c) for each  $i \in \{1, \dots, n\}$  and for each  $g \in C_i$ , select up to  $m$  candidate parents from  $C_1 \cup \dots \cup C_n$ ; and

15 (d) compute an optimal gene network model using Theorem 1.2.

8. The method of claim 1, wherein said algorithm comprises the steps:

- (a) group genes in  $G$  in groups  $C_i$  with  $|C_i| \leq c$  and sort them according to biological knowledge:  $C_1, \dots, C_n$ ;
- (b) for each  $i \in \{1, \dots, n\}$  and for each gene  $g \in C_i$ , select up to  $m$  candidate parents from  $C_1 \cup \dots \cup C_i$ ; and
- (c) compute an optimal gene network model using Theorem 2.

9. The method of claim 1, wherein said algorithm comprises the steps:

- 25 (a) compute  $F(g, \emptyset) = s(g, \emptyset)$  for all  $g \in G$ ;
- (b) for all  $A \subseteq G$ ,  $A \neq \emptyset$  and all  $g \in G$  compute  $F(g, A)$  as  $\min\{s(g, A), \min_{a \in A} F(g, A - \{a\})\}$ ;
- (cc) set  $M(\emptyset) = \emptyset$ ;
- (d) for all  $A \subseteq G$ ,  $A \neq \emptyset$ , do the following two steps:

30 (i) compute  $g^* = \arg \min_{g \in A} (F(g, A - \{g\}) + Q^{A - \{g\}}(M(A - \{g\})))$ ; and

(ii) For all  $1 \leq i < |A|$ , set  $M(A)(i) = M(A - \{g^*\})(i)$ , and  $M(A)(|A|) = g^*$

\*; and

(e) return  $Q^G(M(G))$ .

10. The method of claim 1, wherein said algorithm comprises the steps:

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5 (a) set  $F''(g, \phi, 1) = \phi, S''(g, \phi, 1) = s(g, \phi)$  for all  $g \in G$ ;

(b) for all  $g \in G$ , all  $A \subseteq G, A \neq N$  and all  $n \leq m$  do the following two steps:

(i) select  $B^* \subseteq A$  from  $\{B \subseteq A \mid B = A \vee B = F''(g, A - \{h\}, p), h \in A, p \leq m\} - \{F''(g, A, p) \mid p < n\}$  such that  $s(g, B^*)$  is minimized; and

(ii) set  $F''(g, A, n) = B^*, S''(g, A, n) = s(g, B^*)$ ;

10 (c) set  $M''(\phi, 1) = \phi$  and  $D''(\phi, 1) = \phi$ ;

(d) for all  $A \subseteq G, \phi$ , and all  $n \leq m$  do the following three steps:

(i) choose a triple  $(g, p, q) \in A \times IN_{sm} \times IN_{sm}$  such that  $score(Q^{A-\{g\}}(M''(A-\{g\}, p), D''(A-\{g\}, p))) + S''(g, A-\{g\}, q)$  is minimized and  $(g, p, q)$  induces a network different from  $Q^A(M''(A, r), D''(A, r))$  for  $r < n$ ;

15 (ii) set  $M''(A, n)(i) = M''(A-\{g\}, p)(i)$  for  $i < |A|$ , and  $M''(A, n)(|A|) = g$ ;

and

(iii) let  $v$  denote  $D''(A-\{g\}, p)$ . Set  $w \in IN^{|A|}$  as  $w_i = v_i$  for all  $I < |A|$  and  $^w|A| = q$  and set  $D''(A, n) = w$ ; and

(e) return  $Q^G(M''(G, i), D''(G, i))$  for all  $i \leq m$ .

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11. The method of any of claims 1-10, wherein reliability of an enumerated gene network, comprising the steps:

25  $N_i$ :

- enumerate the most likely gene network models  $N_i$ ,  $1 \leq i \leq n$ ;
- for every  $g, h \in OG$ , count the occurrences of the edge  $(g, h)$  in the networks
- select all edges  $(g, h)$  with at least  $c$  occurrences;
- for all subsets  $M$  of the set of selected edges with  $|M| = k$ , count the networks including all edges in  $MI$ ; and
- return all motives  $M$  with at least  $c$  occurrences.

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12. The method of any of claims 1-11, further comprising calculating a scoring function selected from the group consisting of BRNC score, BDe score and MDL score.

35 13. A method for determining a gene network as substantially described herein.

14. A storage medium containing results obtained using the method of any of claims 1-11.

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5 15. A storage medium containing results obtained using a method as substantially described herein.

16. A system for determining gene network relationships, comprising:  
an input device for providing quantitative expression data for genes of an organism;  
10 a storage device adapted to receive quantitative expression data for genes of said organism;  
a processor adapted to carryout a Bayesian network analysis of network relationships between said genes, thereby producing a data set reflecting said network relationships; and an output device for displaying said data set of said network relationships.

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17. A system for determining gene network relationships as substantially described herein.